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Frank L. Setliff
University of Arkansas at Little Rock

Maximillia M. Muguluma
University of Arkansas at Little Rock

Jody Z. Caldwell
University of Arkansas at Little Rock

PREPARATION OF A SERIES OF SUBSTITUTED N-PHENYL-5-BROMO-2-CHLORO- AND 5-BROMO-6-CHLORONICOTINATES OF POTENTIAL AGRICULTURAL INTEREST

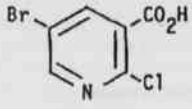
FRANK L. SETLIFF, MAXIMILLIA M. MUGULUMA, and JODY Z. CALDWELL
Department of Chemistry
University of Arkansas at Little Rock
Little Rock, AR 72204

ABSTRACT

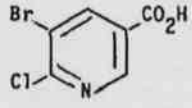
Substituted phenyl esters of 5-bromo-2-chloronicotinic acid and 5-bromo-6-chloronicotinic acid were prepared. The acids were first converted to their respective acid chlorides using thionyl chloride, and the acid chlorides were immediately transformed to the esters by treatment with the appropriately substituted phenol in sodium hydroxide solution. A unique chloride displacement of bromide was observed on attempting to convert 5,6-dibromonicotinic acid to its acid chloride.

INTRODUCTION

A recent paper (Setliff, *et al.*) related our continuing interest in the preparation of dihalonicotinic acid derivatives with potential herbicidal, fungicidal, or ascaricidal activity. As an extension of this work, we now describe the preparation of a series of substituted phenyl esters of 5-bromo-2-chloronicotinic acid (I) and 5-bromo-6-chloronicotinic acid (II) (Setliff, 1970). These compounds comprise the first series of esters with suspected activity synthesized by our group.



I

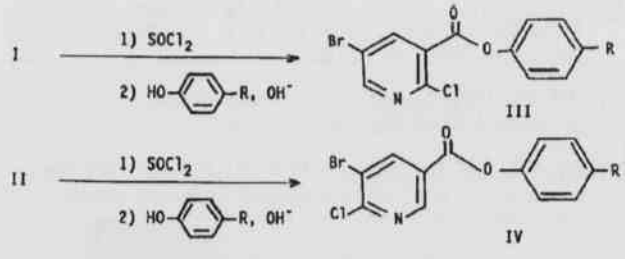


II

MATERIALS AND METHODS

The phenyl 5-bromo-2-chloronicotinates (III) and the phenyl 5-bromo-6-chloronicotinates (IV) were generated by treating the acid chlorides of I and II with the appropriately substituted phenol in basic solution. The acid chlorides were prepared in the normal manner from the acids by use of thionyl chloride. The preparative sequence is summarized in Scheme I below.

Scheme I



Acids I and II were prepared in our laboratory as previously described (Setliff, 1970). The substituted phenols were purchased from Aldrich Chemical company and were technical grade. Melting points were taken on a Mel-Temp apparatus and were uncorrected. Infrared spectra were taken on a Perkin-Elmer 1430 Spectrophotometer equipped with a Model 7300 data station, and samples were prepared as KBr disks. Proton nuclear magnetic resonance spectra were determined on a Varian EM360 instrument with samples dissolved in deuteriochloroform and with tetramethylsilane as the internal standard. Carbon, hydrogen, nitrogen, elemental analyses were performed by Desert Analytics Inc., Tuscon, Arizona.

The following procedure was used to prepare the phenyl esters III and IV. The dihalonicotinic acid I or II (0.500g; 0.002 mol) and thionyl chloride (3 mL) were stirred under gentle reflux for 30 min. During this time the acid completely dissolved. The reaction mixture was cooled to room temperature, and the excess thionyl chloride was removed under reduced pressure on a rotary evaporator (oil bath 50°C). The residual viscous oil (the acid chloride) was used to prepare the ester without further purification. The appropriate substituted phenol (0.015 mol) was dissolved in 5 mL of 0.1 M sodium hydroxide, and the resulting solution was added to the acid chloride. The mixture was stirred vigorously at room temperature for one hour, and then a mixture of ice (5 g) and water (20 mL) was added while stirring was continued. In most cases the ester precipitated. In some cases precipitation was induced by the addition of 10-15mL of cold ethanol to the ice water mixture. The crude ester was collected by vacuum filtration and washed with cold water, followed by ice cold ethanol, and then recrystallized from a small volume of ethanol. Melting points and yields (overall from the acids) are listed in Tables 1 and 2.

Table 1. Experimental, Infrared, and Elemental Analysis Data for the Substituted Phenyl 5-Bromo-2-chloronicotinates (III)

R	% Yld.	MP °C	IR, ν, cm⁻¹		Elemental Analysis Calc'd % (Found %)		
			C=O	C-O-Ar	C	H	N
a. H	61	91	1748	1257	46.08(46.38)	2.24(2.26)	4.48(4.41)
b. Cl	43	103	1752	1279	41.49(41.49)	1.72(1.66)	4.03(3.88)
c. Br	51	120	1734	1282	36.78(36.50)	1.53(1.45)	3.57(3.53)
d. OCH_3	40	73	1733	1262	45.41(45.48)	2.91(2.60)	4.07(4.01)
e. NO_2	42	216	1749	1275	40.28(40.59)	1.67(1.47)	7.83(7.62)

Table 2. Experimental, Infrared, and Elemental Analysis Data for the Substituted Phenyl 5-Bromo-6-chloronicotinates (IV)

R	% Yld.	MP °C	IR, ν, cm⁻¹		Elemental Analysis Calc'd % (Found %)		
			C=O	C-O-Ar	C	H	N
a. H	45	123	1738	1283	46.08(46.19)	2.24(2.09)	4.48(4.39)
b. Cl	43	116	1741	1298	41.49(41.26)	1.72(1.69)	4.03(3.90)
c. Br	45	124	1743	1297	36.78(36.66)	1.53(1.49)	3.57(3.51)
d. OCH_3	55	151	1735	1284	45.41(45.51)	2.91(2.71)	4.07(4.16)
e. NO_2	40	166	1731	1298	40.28(40.36)	1.67(1.49)	7.83(7.66)

Preparation of a Series of Substituted N-Phenyl-5-Bromo-2-Chloro- and 5-Bromo-6-Chloronicotinates

RESULTS AND DISCUSSION

Five Substituted phenyl esters were prepared from each of the acids I and II. As noted in Tables 1 and 2, overall product yields from the acids are marginally adequate. Longer reaction times and or heating showed no improvement, and in some cases heating only diminished the yields due to saponification of the esters.

A comparison of the melting points of the isomerically substituted esters reveals that the 5,6-dihaloesters (Table 2) tend to melt higher than their 2,5-dihalo analogs (Table 1) with the exception of the nitro series. In this series the 4-nitrophenyl 5-bromo-2-chloronicotinate (IIIe) melts 50° higher than the corresponding 4-nitrophenyl 5-bromo-6-chloronicotinate (IVe), suggesting a very efficient type of intermolecular association in the crystalline state of the former. These nitro compounds are strong candidates for single crystal X-ray analysis.

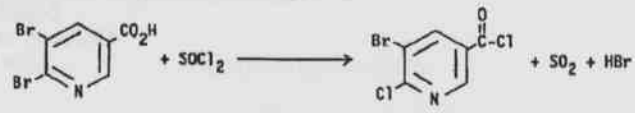
Elemental analysis of all compounds were very satisfactory with percentages falling within acceptable limits of the calculated values. Examination of the infrared spectra revealed the expected absorption bands for both the carbonyl group and carbon to oxygen single bond of the ester functionality. These absorption frequencies are summarized in Tables 1 and 2.

Proton nmr spectra (in $CDCl_3$) were consistent with expected structures. The aromatic pyridine protons appeared downfield from the benzene aromatic protons, and were clearly separated. An interesting comparison is drawn from the spectra of the isomeric methoxy esters III (R = OCH_3) and IV (R = OCH_3), as summarized in Table 3. Most noteworthy is the change in chemical shift of the proton adjacent to the ring nitrogens (H_2 or H_6) in the pyridine ring. This proton becomes more deshielded in compound IVd, when it is *ortho* to the ester carbonyl than in compound IIId, when it is *para* to the ester carbonyl. This is reflected in a downfield shift from 8.70 ppm δ in IIId to 9.35 ppm δ in IVd. Proton H_4 is unaffected by the interchange of chlorine at H_2, H_6, and its chemical shift remains constant at 8.90 ppm δ. The comparisons in Table 3 are typical of all isomeric sets of III and IV esters.

Table 3. A Comparison of the Proton NMR Spectra of the Methoxy Esters IIId and IVd

Cpd.	Pyridine Protons		Benzene Protons		Methoxy Protons
	H_4	H_2 or H_6	H_2	H_3	O-CH_3
IIId	δ 8.90 ppm	δ 8.70 ppm	δ 7.45 ppm	δ 7.10 ppm	δ 3.90 ppm
	d (J=2 Hz)	d (J=2 Hz)	d (J=8 Hz)	d (J=8 Hz)	s
IVd	δ 8.90 ppm	δ 9.35 ppm	δ 7.45 ppm	δ 7.10 ppm	δ 3.90 ppm
	d (J=2 Hz)	d (J=2 Hz)	d (J=8 Hz)	d (J=8 Hz)	s

It was our original intent to also synthesize the analogous esters of 2,5-dibromonicotinic acid and 5,6-dibromonicotinic acid by an identical procedure. When 5,6-dibromonicotinic acid was refluxed with thionyl chloride, the thionyl chloride removed, and the residual acid chloride treated with a basic solution of phenol, there resulted the 5-bromo-6-chloro phenyl ester rather than the expected 5,6-dibromo phenyl ester. We conclude that during the conversion of the acid to the acid chloride there was concurrent displacement of bromine in the 6- position by chlorine as shown below:



This halogen exchange was presumably acid catalyzed by the HCl generated during the reaction. Acid catalyzed displacement of bromine in the 2 or 6 position of pyridine systems has been well documented (Mertel, 1961). That such HCl-catalyzed displacement could have occurred was supported by the fact we observed (by separate experiment) that refluxing 5,6-dibromonicotinic acid in methyl ethyl ketone for 30 minutes with a catalytic amount of 2.5% HCl (aq) caused rapid production of 5-bromo-6-chloronicotinic acid (Caldwell, 1990). The boiling points of methyl ethyl ketone and thionyl chloride are both 78°C, thus identical thermal conditions and reaction times (30 min.) were achieved. Investigation of other plausible mechanistic pathways of the halogen exchange will be carried out at a later date.

In the 2,5-dibromonicotinic acid case, it appears that some displacement of bromine in the 2- position occurs, but not 100%. Treatment of this acid with thionyl chloride, followed by aniline results in a mixture of a dibromo and a bromochloro anilide (Caldwell, 1990). This suggests that the steric effect of the carbonyl group *ortho* to the bromine retards displacement of bromide.

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